WO 2005/085250

PCT/GB2005/000767

101

CLAIMS

- 1. A compound of formula (I):
- 5 PBD-A-Y-X-(Het)<sub>na</sub>-L-(Het)<sub>nb</sub>-L-(Het)<sub>nc</sub>-T-(Het')<sub>nd</sub>-L-(Het')<sub>ne</sub>-L-(Het')<sub>nf</sub>-X'-Y'-A'-PBD' (I)

and salts, solvates, chemically protected forms, and prodrugs thereof, wherein

- with the bonds at the 8 position on each molecule bond to the A and A' groups respectively.
  - the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;
  - ${
    m R}^2$  and  ${
    m R}^3$  are independently selected from -H, -OH, =O, =CH2, -CN,
- 15 -R, OR, halo, =CH-R, O-SO<sub>2</sub>-R, CO<sub>2</sub>R and COR;
  - $R^6$ ,  $R^7$  and  $R^9$  are independently selected from H, R, OH, OR, SH, SR, NH<sub>2</sub>, NHR, NRR', nitro, Me<sub>3</sub>Sn and halo; where R and R' are independently selected from optionally substituted  $C_{1-7}$  alkyl,  $C_{3-20}$  heterocyclyl and  $C_{5-20}$  aryl groups; or
- 20  $R^6$  and  $R^7$  together form a group -O-(CH<sub>2</sub>)<sub>p</sub>-O-, where p is 1 or 2;  $R^{10}$  is a nitrogen protecting group and  $R^{15}$  is either O- $R^{11}$ , where  $R^{11}$  is a hydroxyl protecting group; or  $R^{15}$  is OH, =O or =S; or

 $R^{10}$  and  $R^{15}$  together form a double bond between C10 and N11;

- A is selected from O, S, NH or a single bond;
  Y is a divalent group such that HY = R, or a single bond;
  X and X' are both either NH or C(=O);
  each Het and Het' is independently an amino-heteroarylenecarbonyl group;
- 30 each L is independently selected from  $\beta$ -alanine, glycine, 4-aminobutanoic acid and a single bond;

WO 2005/085250 PCT/GB2005/000767

102

T is a divalent linker group of the form:

$$-NH-Q-NH-$$
 or  $-C(=0)-Q-C(=0)-$ 

wherein Q is a divalent group such that HQ = R; A', Y', Het',  $R^{2'}$ ,  $R^{3'}$ ,  $R^{6'}$ ,  $R^{7'}$ ,  $R^{9'}$ ,  $R^{10'}$ ,  $R^{11'}$  and  $R^{15'}$  are all independently selected from the same lists as previously defined for A, Y, Het,  $R^2$ ,  $R^3$ ,  $R^6$ ,  $R^7$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$  and  $R^{15}$  respectively; na, nb, nc, nd, ne and nf are each independently 0 to 5 and the sum na + nb + nc + nd + ne + nf is 0 to 16.

- 10 2. A compound according to claim 1, wherein the sums na + nb + nc and nd + ne + nf are equal.
  - 3. A compound according to either claim 1 or claim 2, wherein Het and Het' are nitrogen containing heteroarylene units.
  - 4. A compound of formula (II):

15

PBD-A-Y-X-(Het)
$$_{ng}$$
-[L-(Het) $_{nh}$ ] $_{nj}$ -X'-Y'-A'-PBD'
(II)

20 and salts, solvates, chemically protected forms, and prodrugs thereof, wherein

the bonds at the 8 position on PBD and PBD' bond to A and A' groups respectively;

- 25 the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;
  - $R^2$  and  $R^3$  are independently selected from -H, -OH, =O, =CH<sub>2</sub>, -CN, -R, OR, halo, =CH-R, O-SO<sub>2</sub>-R, CO<sub>2</sub>R and COR;
  - ${
    m R}^6$ ,  ${
    m R}^7$  and  ${
    m R}^9$  are independently selected from H, R, OH, OR, SH,
- 30 SR, NH2, NHR, NRR', nitro, Me $_3$ Sn and halo; where R and R' are

WO 2005/085250 PCT/GB2005/000767

103

independently selected from optionally substituted  $C_{1-7}$  alkyl,  $C_{3-20}$  heterocyclyl and  $C_{5-20}$  aryl groups; or

 $R^6$  and  $R^7$  together form a group -O-(CH<sub>2</sub>)<sub>p</sub>-O-, where p is 1 or 2;  $R^{10}$  is a nitrogen protecting group and  $R^{15}$  is either O- $R^{11}$ , where

 $S R^{11}$  is a hydroxyl protecting group; or

 $R^{15}$  is OH, =O or =S; or

35

 ${\bf R}^{10}$  and  ${\bf R}^{15}$  together form a double bond between C10 and N11; A is selected from O, S, NH or a single bond;

Y is a divalent group such that HY = R, or a single bond;

- each Het is independently an amino-heteroarylene-carbonyl group; each L is independently selected from  $\beta$ -alanine, glycine, 4-aminobutanoic acid and a single bond; A', Y', R2', R3', R6', R7', R9', R10', R11' and R15' are all independently selected from the same lists as previously defined
- for A, Y, Het, R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>15</sup> respectively; ng is 1 to 5, nh is 1 to 5 and nj is 0 to 3

  X and X' are either NH and C(=0) respectively or C(=0) and NH respectively.
- 20 5. A compound according to claim 4, wherein the total number of Het groups in the compound represented by the sum  $ng + (nj \times nh)$ ) is 1 to 3.
- 6. A compound according to either claim 4 or claim 5, wherein 25 Het are nitrogen containing heteroarylene units.
  - 7. A compound according to any one of the preceding claims, wherein PBD and PBD' are the same.
- 30 8. A compound according to any one of the preceding claims, wherein  $R^9$  and  $R^{9'}$  are H.
  - 9. A compound according to any one of the preceding claims, wherein  $R^2$ ,  $R^3$ ,  $R^{2'}$  and  $R^{3'}$  are independently selected from R and H.

WO 2005/085250 PCT/GB2005/000767

104

- 10. A compound according to any one of the preceding claims, wherein  $R^6$  and  $R^{6'}$  are independently selected from H, OH, OR, SH, NH<sub>2</sub>, nitro and halo.
- 5 11. A compound according to any one of the preceding claims, wherein  $R^7$  and  $R^{7'}$  are independently selected from H, OR, SH, SR, NH<sub>2</sub>, NHR, NRR' and halo.
- 12. A compound according to any one of the preceding claims, wherein  $R^{10}$  and  $R^{15}$  together form a double bond between N10 and C11 and  $R^{10'}$  and  $R^{15'}$  together form a double bond between N10' and C11'.
- 13. A compound according to any one of claims 1 to 11, wherein  $R^{10}$  and  $R^{10'}$  are independently selected from H, BOC, Troc and alloc, and  $R^{11}$  and  $R^{11'}$  are independently selected from OH, THP or a silyl oxygen protecting group.
- 14. A compound according to any one of claims 1 to 13 for use in 20 a method of therapy.
  - 15. A pharmaceutical composition containing a compound of any one of claims 1 to 13, and a pharmaceutically acceptable carrier or diluent.
  - 16. Use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for treating a proliferative disease.

25

30 17. A method of treatment of a proliferative disease, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound of any one of claims 1 to 13.